# Benzodiazepine prescribing guideline adherence and misuse potential in Irish minors

## Introduction

Benzodiazepine misuse and prescribed benzodiazepine use can have adverse consequences if chronically used. The acute effects of benzodiazepines can include muscle weakness, episodic memory impairment, and paradoxical disinhibition [1]. Chronic use is associated with visuospatial and verbal learning impairment, depressive symptoms and increased suicide risk [1-4]. In Ireland the Benzodiazepine Committee published the Good Practice Guidelines for Clinicians in August 2002 [5]. These guidelines sought to promote safe benzodiazepine prescribing by providing recommendations on prescribing.

## Aim of the study

The aim of this study is to evaluate the prescribing of benzodiazepines to minors in Ireland relative to Good Practice Guidelines for Clinicians.

## Ethical approval

Ethical approval was sought and granted from the Clinical Research Committee of the Cork Teaching Hospitals.

## Method

Data for medicines dispensed between January 2009 and December 2012 was obtained from the Primary Care Reimbursement Service (PCRS) using the Health Intelligence Ireland (HII) database [6]. Information was collected about government-subsidised community-pharmacy-dispensed benzodiazepines. The database includes personal and prescription information, without diagnostic information.

In this study, (i) benzodiazepines are defined as; any drug in World Health Organisation's Anatomical Therapeutic Classification (WHO-ATC) groups N05BA for anxiolytics, and N05CD/N05CF for hypnotics and, (ii) dispensing data are used as a surrogate for consumption data. Dispensing data could not be calculated directly as some (25.9% of population in 2011) are not enrolled in reimbursement schemes. The

consumption level for this group was inferred from the consumption level of similar patients in reimbursement schemes.

The Good Prescribing Practice for Clinicians guidelines which relate specifically to minors (aged less than 18 years) are:

1) Benzodiazepines should be prescribed only for as long as is necessary, aiming for the shortest possible time but no longer than 4 weeks.

2) The long-term risks of using benzodiazepines need to be balanced against the benefits. If a decision to prescribe maintenance benzodiazepines is made then the following recommendation is suggested; Issue small quantities at a time (usually not more than one-week supply).

Consumption of benzodiazepines was quantified in terms of Defined Daily Dose (DDD). As some patients may not have received their prescription at the start of the month, receiving greater than four weeks treatment was based on receiving greater than 28 DDD over two consecutive months. The Mann-Whitney U test was performed on non-normally-distributed continuous/interval data. For categorical data, Pearson's chi-square analysis was performed. A significance level of $\alpha=0.05$ was used. All statistical analyses were performed using Predictive Analytics SoftWare Statistics (PASW; SPSS Inc. Chicago, Ill.) version 18.0.

## Results

### Patient and benzodiazepine consumption data

There were 14,916 minors who received 51,222 items (on 46,208 prescriptions) in the period from 2009 to 2012 inclusive. The majority of prescriptions (90.0%) had a single benzodiazepine dispensed, with 9.4% containing two, and 0.6% containing three or four, benzodiazepine items. Patients who received a single benzodiazepine prescription accounted for 63.9% (n=9,535) of all patients. The median consumption of benzodiazepines per patient was 5.3 DDD (IQR=2.5-17.9). Diazepam was the benzodiazepine with the highest consumption between 2009 and 2011, while in 2012, clobazam had the highest consumption. The majority of patients were only prescribed anxiolytics (60.9%, n=9086), while a smaller percentage were prescribed both anxiolytics and hypnotics (10.6%, n=1583). The percentage of male patients (49.1-

51.0%) was similar during the years 2009-2012 ($\chi^2$=3.487, p=0.359). There were no differences in the percentages of 0-4 year olds, 10-14 year olds, and 15-17 year olds however the percentage of 5-9 year olds decreased in 2011 compared with 2009 and 2010 ($\chi^2$=17.851, p=0.037). Total benzodiazepine prescribing increased by 10.2% (181,264.6 to 199,689.2 DDD) between 2009 and 2012, in contrast to hypnotic consumption which decreased 9.2% (74,856.8 to 67,933.7 DDD) during the same period. The increase in total prescribing observed was due to the 23.8% increase in anxiolytic prescribing (106,407.7 to 131,755.5 DDD). A full breakdown of benzodiazepine prescribing is presented in Table 1. Benzodiazepine prescribing in patients ranged between 5,073.0 DDD (less than 1 year-old) and 125,930.9 DDD (17-18 years-old) over the study period. Prescribing increased with age with an increase of 56.4% in prescribing between 15 and 16 year olds and an increase of 72.8% between 16 and 17 year olds.

INSERT TABLE 1 HERE

**Benzodiazepine guideline 1: "Benzodiazepines should be prescribed only for as long as is necessary, aiming for the shortest possible time but no longer than 4 weeks"**

Almost 15% of patients were prescribed benzodiazepines for greater than four weeks and thus were outside guideline 1, while the majority of patients (85.3%, n=1175) were prescribed benzodiazepines within guidelines. Of those patients outside the guidelines, there were a greater percentage of males (16.0%) than females (13.4%, 1253) ($\chi^2$=19.237, p<0.001). A greater percentage of those who had been prescribed a hypnotic (23.5%, 1372) had received over four weeks of benzodiazepines than those who had not been prescribed a hypnotic (9.0%, n=821) ($\chi$ =594.035, p<0.001).

**Benzodiazepine guideline 2: "Issue small quantities at a time (usually not more than one-week)"**

Approximately half (51.4%) of those who were in breach of guideline 1 also contravened benzodiazepine prescribing guideline 2; the prescriptions were not split into smaller dispensings. There were 15 patients (0.7%) whose prescribing was within guideline 2. The remaining patient received a portion of their prescriptions in accordance with guideline 2. There was no statistical difference in the percentage of males and females who were issued benzodiazepines for greater than 7 days ($\chi^2$=2.022, p=0.568). More than half

of those (58.5%) who were issued a hypnotic received their benzodiazepines in contravention to guideline 2, compared with fewer than half of those only prescribed an anxiolytic (47.2%) ($\chi^2$=32.546, p<0.001).

## Discussion

This study examined benzodiazepine prescribing to people under the age of 18 years in Ireland from 2009-2012 in the context of the Good Practice Guidelines for Clinicians [5]. Most benzodiazepine prescribing was in compliance with the guidelines, and this should be commended. Approximately one in every seven young people who was prescribed benzodiazepines received a prescription for greater than four weeks' supply. Hypnotic consumption fell by nearly 10%, but overall benzodiazepine consumption increased. The rise in overall consumption is worrying because of the long-term potential side effects of regular benzodiazepine use. There was an increase in median benzodiazepine dispensing among Norwegian 15-16 year olds between 2006 and 2010, while in Australians aged 15-24 years, dispensing decreased by approximately half between 2003 and 2006 [7, 8]. Neither study suggested reasons for their change in dispensing patterns.

For those prescribed benzodiazepines for greater than four weeks, the majority were male (53.6%). This result is unexpected, as anxiety, for which benzodiazepines are most commonly prescribed, affects women to a greater degree than men [9]. A possible explanation for this difference is prescribing for epilepsy in males, as there is a higher prevalence of epilepsy among males [10]. This could also explain the doubling in prescribing of clobazam between 2009 and 2012. Another possibility is that more males could be misusing benzodiazepines. The potential for iatrogenic benzodiazepine dependence to develop in a short period of time should not be underestimated. Accordingly, guideline 2 recommends that those who are prescribed benzodiazepines for greater than a month should have their prescriptions issued in quantities of not greater than one week. Over half of patients (51.4%) were prescribed all their medicines in quantities greater than one week while only 0.7% were compliant with the guideline. Future iterations of the guidelines should consider the growing use of clobazam and its legitimate long-term use as an adjunctive therapy in epilepsy.

The main weakness of this study is that the HII database does not differentiate between those taking benzodiazepines for psychologically-based illnesses, with potential misuse, and those who were not. Another limitation was the lack of data on adherence to the prescribed medicines. It is not possible to know whether a prescribed medicine has been taken by the patient at the time of dispensing, stockpiled, with the unintentional possibility of misuse by family members, or diverted for commercial gain. Notwithstanding these points, the data were derived from a nationwide reimbursement database and would not be subject to errors in patient recall. The authors did not have access to population data covering the study period so it not possible to ascertain if the increase in dispensing is due to an increased number of minors.

## Conclusion

Prescribing of benzodiazepines to young people was mostly complaint with guidelines, however compliance was not total. The consequences of this can include lifelong benzodiazepine usage and increased burden upon the Irish healthcare system. It would be prudent to further investigate the reasons for not complying to the guidelines so that inventions may be developed to improve adherence in the future.


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## Conflict of interests

The authors declare that they have no conflict of interest.

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table
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**Table 1. Benzodiazepine prescribing levels (in DDDs and percentage of total benzodiazepine level) on government-subsidised schemes in Ireland between 2009 and 2012**

| Benzodiazepine (with ATC code) | Year | | | |
|---|---|---|---|---|
| | 2009 | 2010 | 2011 | 2012 |
| Diazepam - N05BA01 | 46700 (25.8%) | 45191 (25.3%) | 52653 (27.7%) | 43304 (21.7%) |
| Chlordiazepoxide - N05BA02 | 920 (0.5%) | 807 (0.5%) | 617 (0.3%) | 596 (0.3%) |
| Potassium clorazepate - N05BA05 | 0 (0%) | 0 (0%) | 0 (0%) | 19 (0.0%) |
| Lorazepam - N05BA06 | 3751 (2.1%) | 3702 (2.1%) | 3120 (1.6%) | 2381 (1.2%) |
| Bromazepam - N05BA08 | 1981 (1.1%) | 1237 (0.7%) | 723 (0.4%) | 685 (0.3%) |
| Clobazam - N05BA09 | 30159 (16.6%) | 40409 (22.6%) | 47688 (25.1%) | 67802 (34.0%) |
| Prazepam - N05BA11 | 860 (0.5%) | 481 (0.3%) | 264 (0.1%) | 273 (0.1%) |
| Alprazolam - N05BA12 | 22036 (12.2%) | 22811 (12.8%) | 15280 (8.0%) | 16697 (8.4%) |
| Anxiolytic total | 106407 (58.7%) | 114638 (64.2%) | 120345 (63.2%) | 131757 (66.0%) |
| | | | | |
| Flurazepam - N05CD01 | 7067 (3.9%) | 5731 (3.2%) | 4384 (2.3%) | 4357 (2.2%) |
| Nitrazepam - N05CD02 | 9722 (5.4%) | 11139 (6.2%) | 19560 (10.3%) | 22371 (11.2%) |
| Flunitrazepam - N05CD03 | 1784 (1.0%) | 951 (0.5%) | 1916 (1.0%) | 1586 (0.8%) |
| Triazolam - N05CD05 | 3268 (1.8%) | 3295 (1.8%) | 2211 (1.2%) | 3695 (1.9%) |
| Lormetazepam - N05CD06 | 1593 (0.9%) | 1081 (0.6%) | 694 (0.4%) | 654 (0.3%) |
| Temazepam - N05CD07 | 2969 (1.6%) | 2136 (1.2%) | 1776 (1.0%) | 819 (0.4%) |
| Midazolam - N05CD08 | 2971 (1.6%) | 3878 (2.2%) | 4286 (2.3%) | 6559 (3.3%) |
| Zopiclone - N05CF01 | 25129 (13.9%) | 19159 (10.7%) | 20034 (10.5%) | 15473 (7.8%) |
| Zolpidem - N05CF02 | 20094 (11.1%) | 16373 (9.2%) | 15077 (8.0%) | 12413 (6.2%) |
| Zaleplon - N05CF03 | 261 (0.1%) | 228 (0.1%) | 35 (0.0%) | 7 (0.0%) |
| Hypnotic total | 74858 (41.3%) | 63971 (35.8%) | 69973 (36.8%) | 67934 (34.0%) |
| | | | | |
| Benzodiazepine total | 181265 | 178609 | 190318 | 199691 |